New radiotherapeutic approaches for improving cure and palliation of lung tumors

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2015

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Chapter 5

Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery

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Radiotherapy and Oncology, Jun 2013; Vol. 107, No. 3, pp. 403-8.

Abstract

Background and purpose: Multiple primary lung cancers (MPLC) are not an uncommon presentation. Current guidelines recommend a curative approach when early-stage MPLC is diagnosed as favorable outcomes have been reported after surgery. We studied outcomes following stereotactic ablative radiotherapy (SABR).

Materials and methods: Following review of imaging and pathology at a multi-disciplinary tumor board, a total of 62 patients were referred for SABR with a diagnosis of synchronous MPLC. SABR was performed for both lesions in 56 patients, while another 6 underwent SABR for only one lesion and surgery for the other lesion. A total dose of 54-60 Gy was delivered in 3-8 fractions.

Results: Median follow-up was 44 months (95%CI: 29-59). Overall survival of all patients was 31 months (95% CI: 17-44), with an actuarial 2-year survival of 56%. No grade 4 or 5 post-SABR toxicity was observed. Local control rates calculated per lesion, were 84% at two years, and 78% at 3 years. The two-year actuarial regional control rate was 87%.

Conclusion: SABR for synchronous MPLC achieves a lesion control rate of 84% after 2 years, with limited toxicity. SABR should be considered when patients with lung cancer present with a synchronous second lesion and no nodal involvement.

Introduction

The reported incidence of multiple primary lung cancers (MPLC) ranges from 3.7-8%, a finding attributed to tobacco carcinogens damaging the entire field at risk [1]. The new 7th International Association for the Study of Lung Cancer (IASLC) Tumor, Node, Metastasis (TNM) staging system classifies synchronous lung tumors arising in the same lobe as T3 (6th TNM version: T4), and synchronous ipsilateral lesions in different lobes as T4 (6th TNM version: M1), as these presentations are associated with different survivals [2]. In addition, the 7th IASLC TNM staging system has added a new classification of M1a, to describe patients with synchronous bilateral lesions, and only lesions with different histology are classified as separate tumors. Early studies distinguished MPLC from metastases based on differences in pathology [3], but recent studies have used techniques such as array comparative genomic hybridization and somatic mutation analysis [4]. However, histology is not readily available in patients presenting with peripheral lung lesions.

The failure to recognize a nodule in the contralateral lung as a potential MPLC may lead to the inappropriate use of a palliative treatment strategy. Surgical publications have reported that resection of all lesions can result in long-term survival [5-9]. However, patients may be unfit for surgery or refuse surgery. Stereotactic ablative body radiotherapy (SABR) is now an established treatment for early-stage lung cancer in medically inoperable or borderline operable patients [10]. Recent studies have reported on the outcomes of a limited number of cases of synchronous MPLC treated using SABR [11;12]. Since the introduction of SABR in our center in 2003, we have routinely treated MPLC in patients who were unfit or unwilling to undergo surgery for one or more lesions. We retrospectively studied all such cases treated at our center.

Material and Methods

Between April 2003 and July 2012, 873 patients were treated with SABR for stage I or IIa lung cancer (according to 7th TNM staging system; or stage I according to 6th TNM) at our center. All patients were referred for SABR after discussion at a multi-disciplinary tumor board, and patient details were

retrieved from our prospective institutional database. Eligible cases had to have a clinical presentation consistent with MPLC on the basis of CT scans and FDG -PET scans, with or without histological evidence.

A total of 62 patients fulfilled our inclusion criteria and were treated with either SABR alone to both lesions (n=56), or surgery for one lesion and SABR for the other (n=6). This cohort represents 7% of our population treated with SABR for early stage lung cancer, and included 31 patients with bilateral lesions (M1a according to 7th TNM), and 31 patients with a second lesion located in the ipsilateral lung (7th TNM: T3 or T4). Of the latter, both lesions were in the same lobe in 16 patients (T3). Pre-treatment histology was obtained in 48% of patients for one lesion, and for both lesions in only 3% of cases (n=2) (Table 1). In the latter group, both patients had the same histology for both tumors. In 6 patients treated by surgery and SABR, resection of one lesion was performed before SABR (4 patients) or after (2 patients). The interval between surgery and SABR was 3 months or less in all cases. Surgical procedures consisted of a lobectomy (n=4), sleeve lobectomy (n=1) and bilobectomy (n=1).

SABR was delivered in an outpatient setting as described previously, using risk-adapted fractionation schemes prescribed to the encompassing isodose [13]. Prescribed doses ranged from 54-60 Gy and were delivered in 3 to 8 fractions. Contouring and planning was performed using a four-dimensional (4D) CT-scan for all patients, with an internal target volume (ITV) encompassing all motion during normal breathing. A margin expansion of 3-5mm was added in all directions to the ITV to derive the planning target volume (PTV). Treatment planning was optimized to limit the dose to the surrounding organs at risk (OAR). Between 2003 and 2008, patient set-up was performed using infrared bodymarkers and orthogonal X-ray imaging (ExacTrac, BrainLab AG, Feldkirchen, Germany) for matching on the bony anatomy. After 2008, set-up was based on the tumor position using cone beam CT-scans (Varian medical systems, Palo Alto, CA, USA). No active motion management was used during delivery. For 10 patients in whom both lesions were located adjacent to each other, SABR was delivered using a single treatment isocenter. In all other patients, SABR was delivered using separate isocenters, and a second CBCT on-line setup.

Follow-up visits, including CT scans of the chest and upper abdomen, took place at 3, 6 and 12 months, and yearly thereafter [14]. FDG-PET-scans were performed only when disease recurrence was suspected. Toxicity was scored using the Common Toxicity Criteria version 4.0. Local (LR) and regional (RR) recurrence and distant metastases (DR) were defined as reported previously [13]. Briefly, LR was defined as progression of the lesion in the proximity of the PTV. Imaging studies with any suspicious findings were discussed in a multidisciplinary board meeting, where a consensus was reached about the differentiation between progression and radiotherapy-induced fibrosis. RR was defined as failures in hilar or mediastinal nodes, and all progression outside the radiation field and regional lymph nodes was defined as DR. If patients were unable or unwilling to attend follow-up visits at our centre, the treating physician was contacted to retrieve follow-up data.

Kaplan-Meier analysis was used to calculate overall survival and local-, regional- and distant control. A sub-analysis was performed to evaluate if there was any difference between the patients with ipsilateral- and bilateral lung lesions. Baseline characteristics of these cohorts were compared using an Independent *t*-test, Mann-Whitney test or Chi-squared test. All statistical tests were performed using SPSS version 20.0.

Results

The patient characteristics are summarized in Table 1. Briefly, most patients were males (66%) with a median age of 72 years, and a median Charlson comorbidity score (CCI) of 5. All patients were staged using a FDG-PET-CT. In 94% of patients, both lesions were PET-positive. In the other patients, only one (n=3) or none (n=1) of the lesions were PET-positive. However in these cases the lesions were growing on consecutive CT-scans. Invasive nodal staging was performed in 13% of patients.

No patient presented with more than 2 tumors, with individual tumors predominately classified as stage Ia or Ib. The median diameter of the first (largest) lesion was 31 mm (range 10-69 mm), with that of the second (smallest) tumor being 15 mm (range 6-42 mm). The corresponding median PTV values were 41 cc (range 8-212 cc) and 12 cc (range 2-77 cc), respectively. The median prescribed dose was 60 Gy for both lesions, delivered with a median of 5 fractions.

Table 1: Tumor and treatment characteristics of patients treated for synchronous tumors, with details for all patients (n=62), and according to lesion distribution (ipsilateral (n=31) or bilateral (n=31)

Variable	Median (range) or n (%)			*p*-value
	Total	Ipsilateral	Bilateral	
Age at diagnosis	72 (48-87)	73 (59-84)	72 (48-87)	0.11[f]
Gender				0.28[d]
Male	41 (66%)	23 (74%)	18 (58%)	
Female	21 (34%)	8 (26%)	13 (42%)	
Performance score	1 (0-3)	1 (0-3)	1 (0-3)	0.89[e]
CCI[a], age-adjusted	5 (2-11)	5 (4-11)	5 (2-9)	0.12[e]
COPD-GOLD[b] classification				0.56[e]
No COPD	12 (19%)	7 (23%)	5 (16%)	
I - II	29 (47%)	13 (42%)	16 (52%)	
III	17 (27%)	11 (35%)	6 (19%)	
IV	4 (7%)	0 (0%)	4 (13%)	
Prior history of malignancy	22 (36%)	11 (35%)	11 (35%)	1.0[d]
Prior history of lung tumor	8 (13%)	4 (13%)	4 (13%)	1.0[d]
Invasive mediastinal staging				0.47[e]
None	54 (87%)	27 (87%)	27 (87%)	
EUS/EBUS[c]	5 (8%)	3 (10%)	2 (7%)	
Mediastinoscopy	3 (5%)	1 (3%)	2 (7%)	
Stage 1st lesion				0.89[e]
Ia	26 (42%)	13 (42%)	13 (42%)	
Ib	31 (50%)	16 (52%)	15 (48%)	
IIa	5 (8%)	2 (6%)	3 (10%)	
Stage 2nd lesion				0.64[e]
Ia	57 (92%)	29 (94%)	28 (90%)	
Ib	5 (8%)	2 (6%)	3 (10%)	
Pathological confirmation				0.82[e]
One lesion	30 (48%)	17 (55%)	13 (42%)	
Both lesions	2 (3%)	0 (0%)	2 (6%)	
Histology				0.43[e]
Adenocarcinoma	10 (16%)	5 (16%)	5 (16%)	
Squamous cell carcinoma	10 (16%)	4 (13%)	6 (19%)	
NSCLC NOS	12 (19%)	8 (16%)	4 (13%)	
Tumor diameter (mm)				
1st lesion	31 (10-69)	33 (15-69)	33 (16-55)	0.72[f]
2nd lesion	15 (6-42)	15 (6-32)	16 (9-40)	0.80[f]

[a] CCI = Charlson comorbidity index, [b] COPD-GOLD classification = Chronic Obstructive Pulmonary Disease - Global Initiative on Obstructive Lung Disease classification (http://www.goldcopd.org), [c] EUS/EBUS = Endoscopic ultrasound / Endobronchial ultrasound, [d] Chi-squared, [e] Mann-Whitney, [f] Independent t-test

The median follow-up was 44 months, calculated by the reverse Kaplan Meier method. Median overall survival was 31 months (95% CI: 17-44 months), with 2-year and 3-year survivals of 56% and 40%, respectively (Fig. 1A). A local recurrence was diagnosed on radiological grounds in eight patients, four of whom had progression in both lesions treated using SABR. Local control rates, calculated per treated lesion, were 84% at two years, and 78% at 3 years (Fig.

1B). A regional tumor recurrence (RR) was observed in 6 patients, three of the latter had relapses in both the hilus and mediastinum. An isolated RR was seen in one patient, while 5 other patients had both local and/or distant recurrence (Fig. 2). The regional control rate (RCR) after 2 years was 87% (Fig 1C). A total of 18 patients developed distant metastases, with the commonest sites being the brain (n=6), liver (n=5), bone (n=5) and lung (n=4). The freedom from distant relapse rate was 73% at 2 years (Fig. 1D). The median disease-free survival was 32 months, with a 2-year actuarial disease free survival rate of 62%. At time of analysis, 36 of the 62 patients had died, of which 20 died due to lung cancer, and 10 of other causes. The exact cause of death was unknown in 6 patients, all of whom were free from disease relapse at the last clinic visit.

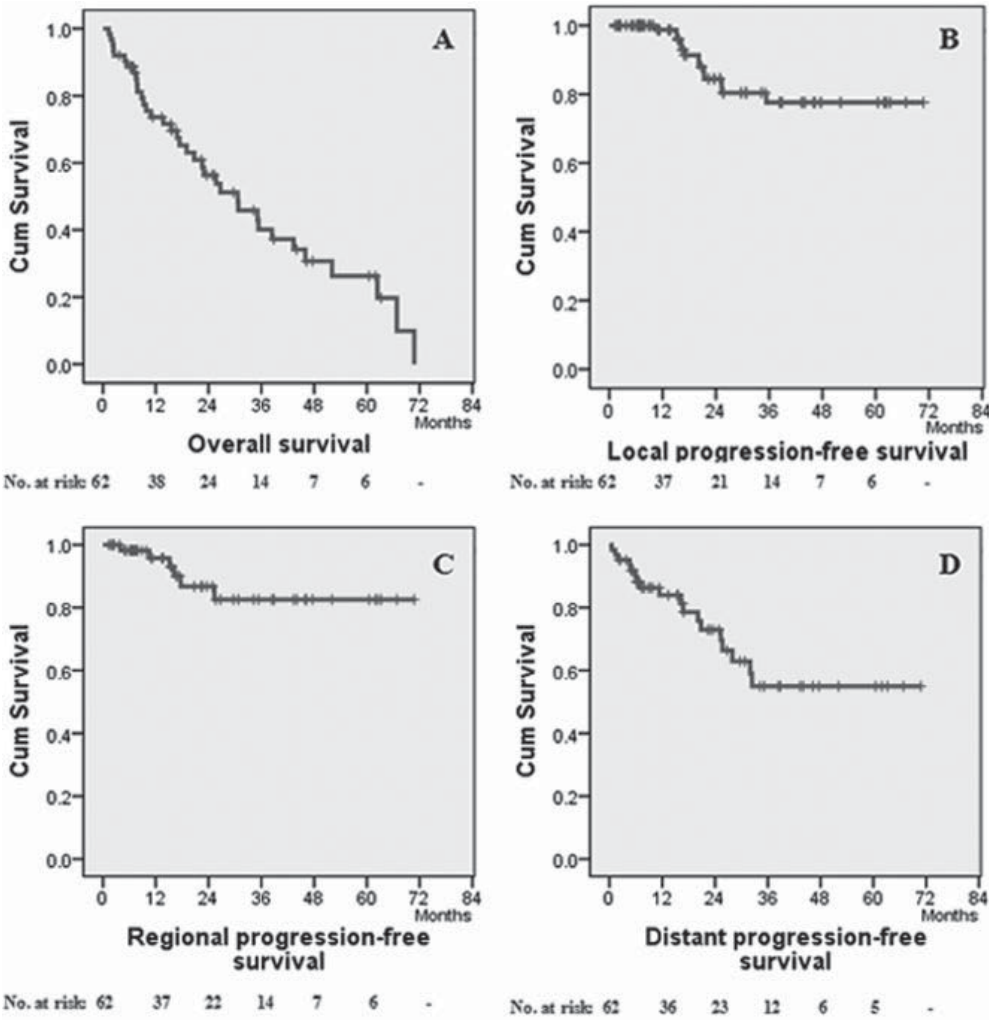

Figure 1. Kaplan-Meier survival curves of entire cohort: (A) overall survival, (B) actuarial local control, (C) actuarial regional control and (D) distant control.

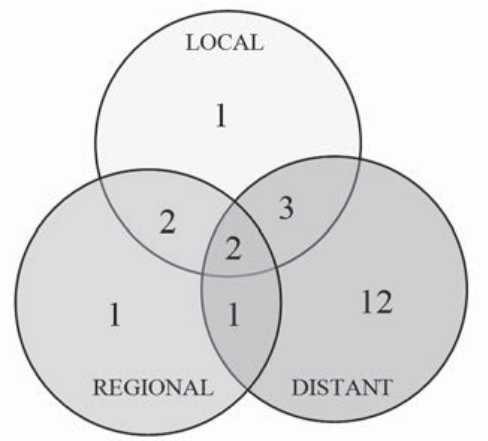

Figure 2. Patterns of recurrence; number of patients with local, regional, distant failure or a combination thereof.

In patients treated with SABR to both lesions, no clinician-scored early side effects were recorded in 49% of the patients, and no early grade ≥3 toxicity was reported for any patient. Reported side effects were similar to previously reported after SABR, and consisted of fatigue (31%), pulmonary complaints (cough, dyspnea) (16%) and local pain (8%). Late side effects were observed in 25 patients, of which only 3 patients (4.8%) experienced grade 3 toxicity with local pain (2 patients) and radiation-induced pneumonitis (one patient). No grade 4 or 5 late side effects occurred after SABR for both lesions. In the six patients who underwent surgery for one lesion, two patients developed high-grade toxicity, namely septicaemic shock requiring resuscitation in one patient, and empyema and broncho-pleural fistula in another patient.

An exploratory analysis compared patient outcomes for lesions located in the ipsilateral lung (classified in the 7th TNM as T3 or T4) or in bilateral lungs (7th TNM: M1a). Baseline characteristics did not significantly differ between the groups (Table 1). Overall survival (p=0.29) and distant failure rates (p=0.58) were not significantly different between ipsilateral and bilateral lesions (Fig. 3A and 3D). However, significant differences in local- and regional control were observed between the two groups, with the local control per lesion at 2 years being 74% versus 92% for ipsilateral and bilateral lesions, respectively (Fig. 3B). The corresponding regional control rates after 2 years were 69% versus 100% for ipsilateral and bilateral lesions (p=0.003) (Fig. 3C). No significant differences in early (p=0.59) or late (p=0.88) toxicity were seen between the two groups.

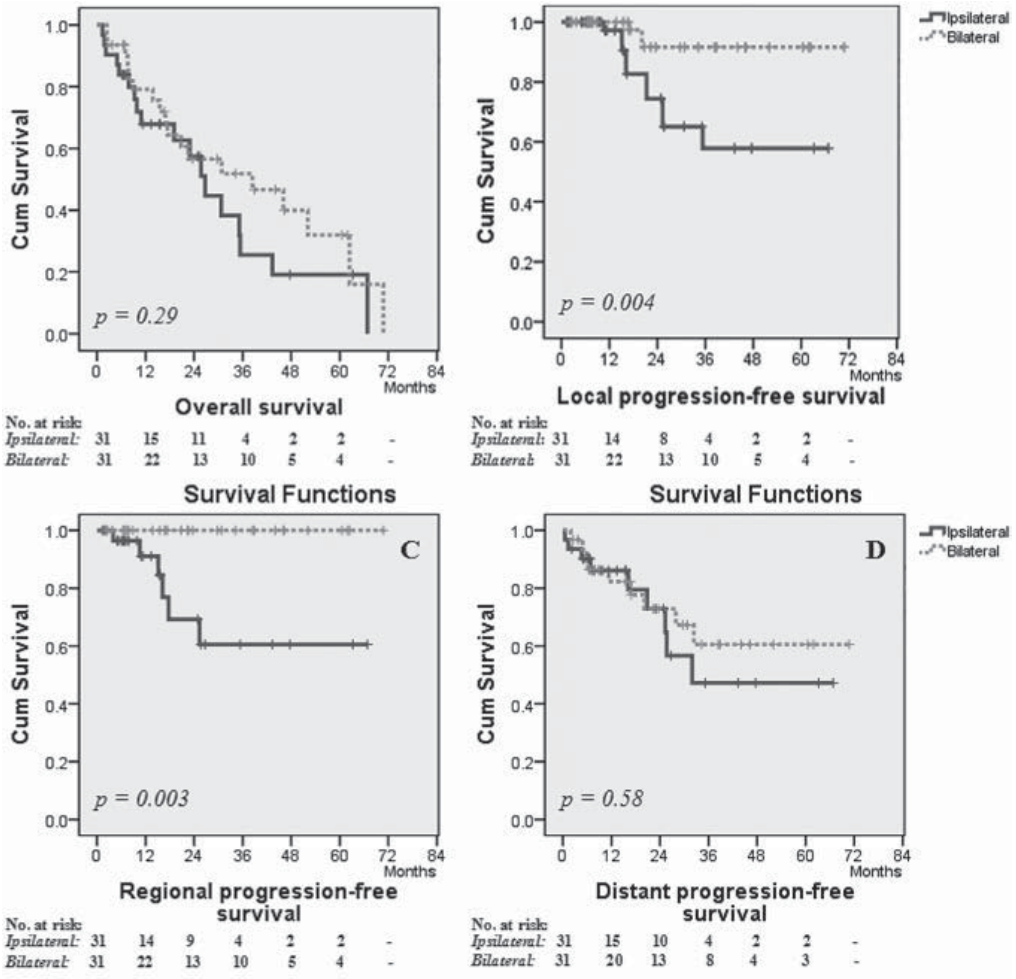

Figure 3. Kaplan-Meier survival curves per tumor location, for ipsilateral (solid grey line) or bilateral (dotted light-grey line) lesions: (A) overall survival, (B) actuarial local control, (C) actuarial regional control and (D) distant control.

Discussion

A curative approach to patients presenting with MPLC is now guideline-specified therapy. For example, ESMO Clinical Practice Guidelines for metastatic NSCLC recommend that after appropriate staging, a solitary lesion in the contralateral lung should be considered as synchronous secondary primary lung tumor, and treated as such [15]. However, the limited data in the radiotherapy literature on MPLC suggest that radiation oncologists may be less likely to follow a curative approach in such a situation. The present report on 62 patients represents the largest series of synchronous early stage MPLC treated with SABR (with or without surgery) to date.

Of note is our finding that the overall survival in this analysis, as well as local control per lesion and distant failure rates, are inferior to what has been reported in patients undergoing SABR for a solitary early-stage NSCLC [13,16]. Nevertheless, it is consistent with a surgical report suggesting that patients with multiple lesions have an almost twofold higher risk of death [17]. Comparisons with the surgical literature on synchronous lung lesions are difficult as our patients were older and had more comorbidity. The largest surgical report on MPLC to date consisted of 92 patients, reported a 2-year overall survival of 80% in patients without any nodal metastases, and approximately 40% when nodal metastases were present [5]. The 2-year overall survival of 56% observed in our population is likely to reflect patients extensive co-morbidity, as well as their lack of invasive lymph node staging.

Differences were observed in local and regional control rates between patients presenting with synchronous bilateral lesions, and those with ipsilateral lesions. In the former, the observed 2-year local and regional control rates per lesion were 92 and 100%, respectively, which are comparable to results reported for SABR to single lesions [13,16]. In contrast, the local and regional control rates were 71 and 69%, respectively, in patients with ipsilateral lesions ($p=0.003$). The reasons for these findings are unclear, but a pooled analysis of surgical reports also reported an inferior survival in patients with MPLC and ipsilateral lesions [18]. The above mentioned authors had hypothesized that bilateral lung lesions may have a higher probability of being true MPLC, instead of being metastases. An alternative explanation may be that post-SABR fibrosis could have been mistaken for recurrence on follow-up CT-scans, as the distinction between fibrosis and recurrent disease can be difficult [19].

Our findings should be interpreted with caution due to the small number of observed events. However, it does suggest that patients with ipsilateral lesions may merit from invasive staging for lymph node metastases. Of the six patients who developed a subsequent regional recurrence, only one received EUS/EBUS prior to treatment. The other 5 patients did not undergo invasive mediastinal staging, as the pre-treatment FDG-PET-scan showed no nodal uptake. Previous studies suggest that despite negative findings on CT or PET-scan, around 10% of patients do have positive lymph nodes after biopsy with endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) [20].

The main limitations of our study are its retrospective nature and the lack of pathological confirmation for primary lesions. However, previous studies have shown that new or growing PET-positive benign lesions are uncommon in the Dutch population [21-23]. In addition, outcomes of SABR in patients with and without known pathology were comparable in our population [16]. Another drawback of the lack of tissue is the inability to distinguish between a second primary tumor and a metastasis. However, the mandatory use of FDG-PET scans ensures that a second lesion would at most be a solitary metastasis. As the survival observed in our patients is superior to that of patients with stage IV NSCLC, and as recent reports show that the aggressive treatment of oligometastatic NSCLC may be justified [24], our approach appears justified in view of the low toxicity of SABR.

In conclusion, patients with a diagnosis of MPLC as established by a multidisciplinary tumor board, are eligible for curative SABR as 2-year overall survival of 56% can be achieved, with less than 5% of patients experiencing grade ≥3 toxicity. The relatively high rate of nodal recurrences in patients who present with multiple ipsilateral lesions suggests that invasive nodal staging may be required for such cases.

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